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A new prognostic marker in small cell lung cancer: red cell distribution width ratio of hemoglobin

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ABSTRACT

Aim: The ratio of hemoglobin (Hb) to red cell distribution width (RDW) (HRR) has been defined as an effective prognostic factor in various cancer types. The aim of this study is to investigate the prognostic role of HRR value in small cell lung cancer (SCLC).

Material and Method: A total of 1039 patients diagnosed with SCLC between 2010-2021 were included in the study. After exclusion of 199 patients without positron emission tomography-computerized tomography (PET-CT), age, gender, additional disease histories, smoking history, pathological stages, survival status, disease progression times, treatments applied, first hemoglobin obtained after diagnosis, red cell distribution width and ratios, and other laboratory parameters of 840 patients were recorded. The log-rank test and the Cox proportional hazards model were used to identify predictors of mortality.

Results: A total of 840 patients were included in the study. The median overall survival (OS) and the progression-free survival (PS) times of the patients were 9 months, and 7 months, respectively. The cut-off value for HRR was determined 0.580 (sensitivity 78.73%, specificity 37.88%). In this study, each one-unit increase in HRR reduces death and survival by 1.6 times detected, and it was revealed that HRR had a statistically significant effect on OS and PS. When the patients were divided into two as limited and extensive disease, there was a statistically significant difference between the groups in terms of OS (12-6 months) and PS (10-6 months), but no significant difference was found in terms of HRR between these two groups.

Conclusion: HRR is an easily accessible, inexpensive parameter that can be used as a prognostic marker in patients with SCLC.

Keywords: HRR, SCLC, survival, prognosis

INTRODUCTION

Small cell lung cancer (SCLC) constitutes approximately 15-20% of all lung tumors (1). It has a poor prognosis due to its faster tumor replication time and thus the early development of distant metastases. Although SCLC responds dramatically to chemotherapy and radiotherapy, overall survival (OS) and progression-free survival (PS) of patients are adversely affected due to tumor resistance or recurrence within one year (2).

In recent years, numerous studies have examined the prognosis of SCLC. A few molecular markers such as Glasgow prognostic score(3), alkaline phosphatase (ALP) (4) and lactate dehydrogenase (LDH) level (5), serum P53 antibody (6) have been confirmed to be associated with mean survival in patients with SCLC; however, these molecular markers are of limited use due to the complex and expensive detection methods thereof. Therefore, it is of great importance to identify more economical, useful, and effective biomarkers to evaluate the prognosis of patients with SCLC.

It was reported that hemoglobin (Hb) value, which reflects the degree of anemia, may be an independent predictor of prognosis in solid organ tumors and hematological malignancies such as lymphoma and multiple myeloma (7). Red cell distribution width (RDW) is an important complete blood count (CBC) parameter used in the diagnosis and differential diagnosis of various types of anemia. It was shown to be closely associated with poor prognosis in cardiovascular and oncological diseases (8,9). High RDW values are associated with an indicator of poor prognosis in patients with lung cancer, breast cancer, esophagus and kidney cancer (10-13). Wherefore Hg and RDW values are affected by many non-neoplastic conditions alone the Hb/RDW ratio (HRR) may be a more independent marker (14).

There are few studies on SCLC due to both the lack of new treatment regimens and simple and effective prognostic factors to evaluate the prognosis (15). In this study, it was aimed to determine that the HRR value, which is an easily

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measurable, repeatable, and inexpensive parameter, is an independent prognostic factor for OS and PS, with the number of patients we think may be sufficient considering this deficiency.

MATERIAL AND METHOD

The study was carried out with the permission of University of Health Sciences, Ankara Atatürk Sanatoryum Training and Research Hospital Clinical Researches Ethics Committee (Date: 22.02.2023, Decision No: 2661). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

SCLC patients diagnosed at Ankara Atatürk Sanatoryum Training and Research Hospital between January 2010 and January 2021 were included in the study. Inclusion criterias are: (i) histopathologically diagnosed SCLC; (ii) adequate imaging data for computed tomography (CT), magnetic resonance imaging device (MRI), and PET-CT tumor staging; (iii) no previous antitumor therapy including radiotherapy, chemotherapy, immunotherapy, and targeted therapy; (iv)routine findings of blood analysis and blood biochemistry, hospital-based laboratory test results. Exclusion criteria are: (i) patients younger than 18 years of age; (ii) patients with non-small cell lung carcinoma; (iii) patients with a secondary malignancy; (iv) patients with comorbid infections, inflammatory diseases, lymphoproliferative diseases, additional diseases such as chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), diabetes mellitus (DM) affecting the RDW value.

1039 SCLC patients were screened. 199 patients who had no PET-CT were excluded from the study, and 840 patients were included in the study. The study was designed retrospectively, no written informed consent form was obtained from patients.

Clinical Data

Clinical data such as age, gender, smoking history, staging, treatment regimens (chemotherapy, radiotherapy), adjuvant therapy, neoadjuvant therapy, operation], diagnosis time, initial HRR values were recorded. The HRR value was calculated using CBC values as follows: Hb(g/dl)/RDW (%).

Tumor Staging

Tumor staging was based on the eighth edition of the staging criteria published by the International Association for the Study of Lung Cancer (16).

Observation Indicators

The following indicators of observation were used: OS was defined as the time from first treatment to death or last follow-up, while PS was defined as the time from the start of first-line chemotherapy to the date of disease progression or death.

Statistical Analysis

Descriptive statistics (mean, standard deviation, minimum, median, maximum) were used to describe continuous variables. The distribution of continuous variables was examined using a Shapiro-Wilk test, and variables with p-levels under 0.05 were considered to have abnormal distribution. Overall survival and progression-free survival were evaluated by the Kaplan-Meier method. The effect of CBC parameters on survival was examined by Cox Regression analysis. The power of CBC parameters to predict death and progression were examined by A Receiver Operating Characteristic (ROC) analysis.Statistical significance level was determined as 0.05. Analyzes were performed using MedCalc® Statistical Software version 19.7.2 (MedCalc Software Ltd, Ostend, Belgium; 2021).

RESULTS

199 patients without PET-CT were excluded from the study, and 840 patients were included. The demographic data and clinical characteristics of the patients were shown in **Table 1**. The majority of the patients were male (n=751, 89.4%). The mean age was 62,2 +9,1 years (25-88). 44.2% (371) of the patients were smokers, and the mean number of packs/year was 40. There was no comorbid disease in 57.5% of the patients. When patients were classified according to tumor size, lymph node metastasis, and distant organ metastasis; 70% of them were in the T4 group; 54.7% were in the N3 group, and 59.6% were in M0. The most common organ with metastasis was bone (n=111, 13.2%) (**Table 1**).

The laboratory parameters of the patients are given in **Table 1**. Mean lymphocyte/C-reactive protein (CRP) ratio (LCR) value was 0.5 (0-361), neutrophil/lymphocyte ratio (NLR) value 3.4 (0-12684.7), platelet/lymphocyte ratio (PLR) value 151.4 (20-54187.2) and HRR value 1.0 (0.3-1, 4). The median OS of the patients was 9 months, and the median PS was 7 months. The effects of LCR, NLR, PLR, CRP/Alb, and HRR values on survival were examined. According to statistical analysis, while the significant effect of LCR was only in overall survival (p=0.03) on the other hand HRR was found to be an expressive effect in both OS and PS (p=0.01) (**Table 2**). The cut-off value of HRR was determined by the ROC analysis as <1.08 and is shown in **Figure 1**. Moreover, it was determined as a remarkable result that each one-unit increase in HRR reduces both mortality and progression by nearly 1.6-fold(**Figure 2**).

Table 1: Demographic Data

	n (%)
Gender	
Male	751 (89.4)
Female	89 (10.6)
Age	62.2 (+9.1)*
Smoking	371 (44.2)
Smoking consumption amount (Pack/year)	48.9(+25.5)*
Tumor Size (mm)	71.2+28.7*
T1	50 (6)
T2	110 (13.1)
T3	88 (10.5)
T4	592 (70.5)
N0	43 (5.1)
N1	34 (4)
N2	304 (36.2)
N3	459 (54.7)
M0	501 (59.6)
M1a	103 (12.3)
M1b	236 (28.1)
Metastasis localizations:	
Bone	111 (13.2)
Opposite Lung	22 (2.6)
Liver	16 (1.9)
Surrenal	25(3)
Brain	10 (1.2)
> Two organs	328 (39.1)
Laboratory parameters:	**Med(min-max)**
Hemoglobin	14(6.8-18.5)
Lymphocyte (103)	1.8(0-5.6)
Neutrophil	6.2(0-51.5)
Platelet	277(31-972)
RDW	14.6(11.8-31.2)
Albumin	4.2(1.9-49.2)
CRP (mg/l)	3.3(0-321.1)
LCR	0.5(0-361)
NLR	3.4(0-12684.7)
Platelet/ Albumin	60.8(1-260.6)
PLR	151.4(20-54187.2)
CRP/ Albumin	0.5(0-65.7)
HRR	1.0(0.3-1.4)

CRP: C-reactive protein, HRR: Hemoglobin/ Red cell distribution width ratio LCR: lymphocyte/CRP ratio, NLR: neutrophil/ lymphocyte ratio PLR: Platelet/ lymphocyte ratio RDW: Red cell distribution width, *: Mean ± SD

Table 2. Effect of LCR, NLR, PLT/ALB, HRR Values on OS and PS

	OS			PS		
	p	HR	95% GA	p	HR	95% GA
LCR	0.038	0.997	0.995-1.00	0.079	0.998	0.995-1.00
NLR	0.798	1.00	1.00-1.00	0.686	1.00	1.00-1.00
Platelet/Alb.	0.627	1.00	0.999-1.002	0.203	1.001	0.999-1.003
PLR	0.988	1.00	1.00-1.00	0.877	1.00	1.00-1.00
CRP/Alb.	0.067	1.020	0.999-1.042	0.133	1.017	0.995-1.040
HRR	0.013	0.605	0.406-0.901	0.019	0.624	0.421-0.925

CRP: C-reactive protein, HRR: Hemoglobin/ Red cell distribution width ratio, LCR: lymphocyte/CRP ratio, NLR: neutrophil/ lymphocyte ratio PLR: Platelet/ lymphocyte ratio

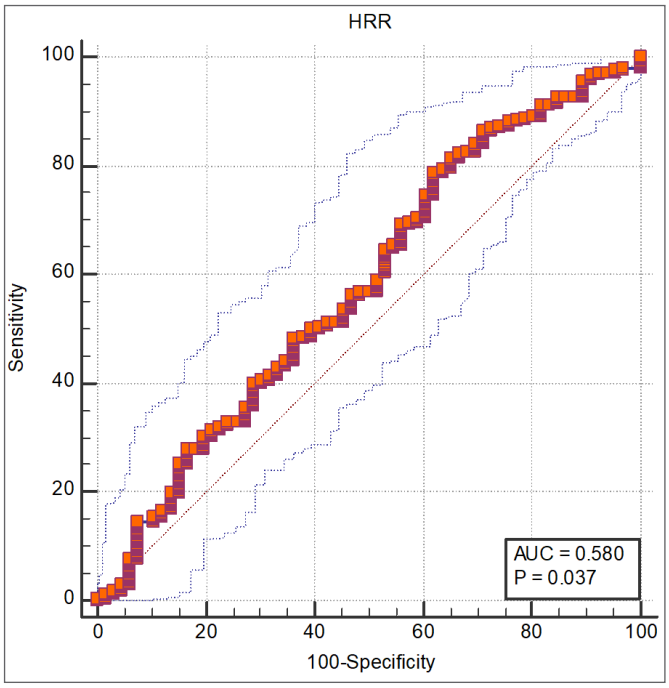

Figure 1: HRR ROC analysis graph

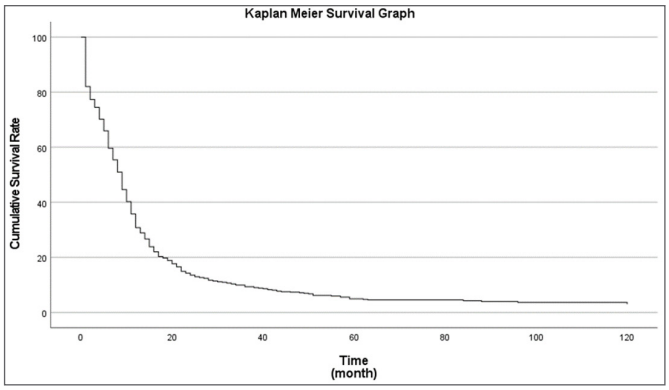

Figure 2: The effect of HRR on OS (Each one-unit increase in HRR reduces mortality by 1.6-fold)

In our study, there was a statistically significant difference between limited and extensive disease in terms of OS (12 /6 months) and PS (10/6 months) (p<0.001), in parallel with the studies performed so far. On the other hand, when laboratory parameters were examined between limited and extensive stages, while there was no difference was found for HRR, but statistically, a significant difference was found for PCR, NLR, and CRP/Alb between the two groups (**Table 3**).

Table 3: Determination of Factors Predicting Progression and Mortality

	AUC	p	Cut-off value	Sensitivity	Specificity
LCR	0.515	0.718	>0.09	83.09	30.77
NLR	0.633	<0.001	>2.93	63.90	63.64
Platelet/Alb.	0.688	<0.001	>39.77	72.08	60.61
PLR	0.581	0.021	>190	34.63	80.30
CRP/Alb.	0.570	0.078	>0.149	77.66	39.39
HRR	0.580	71	<1.08	78.73	37.88

CRP: C-reactive protein, HRR: Hemoglobin/ Red cell distribution width ratio, LCR: lymphocyte/CRP ratio, NLR: neutrophil/ lymphocyte ratio PLR: Platelet/ lymphocyte ratio

DISCUSSION

While the prognosis of patients with non-small cell lung cancer (NSCLC) has greatly improved with recent advances in molecular biology techniques and the advent of targeted drugs and immunotherapy, the survival of patients with SCLC has not changed due to the lack of both new treatment regimens and simple-effective prognostic factors to assess the prognosis. Therefore, it is essential to find new and effective prognostic indicators to improve the prognosis of patients with SCLC. Studies have confirmed that HRR is associated with the prognosis of patients with esophageal (17), head and neck tumors (18), and NSCLC (19), whereas the number of studies on patients with SCLC is very few (20).

Although there are studies showing the prognostic values of RDW and hemoglobin separately in patients with lung cancer, studies showing the prognostic effect of HRR on lung cancer are limited. In the first study conducted with HRR by Sun et al. (17) in 362 patients receiving curative treatment for esophageal cancer, hemoglobin and RDW alone were not found to be significant in terms of survival, while HRR was found to be predictive for overall survival. Bozyaka et al. (19) reported that low HRR value may be an independent predictor factor of overall survival in their study consisting of 153 patients with advanced NSCLC. In another study by Petrella et al. (14) 349 patients with a diagnosis of lung adenocarcinoma who were undergone operation were included in the study. It has been reported that the preoperative HRR value is an effective prognostic factor together with pathological lymph node involvement for disease-free survival in resected patients.

The first study by Wu et al. (20), showing the prognostic importance of HRR in SCLC, was conducted with a total of 146 patients, and the cut-off value for HRR was found to be 0.985. OS was determined as 9 and 17.5 months in the low and high HRR groups, respectively, and PS as 5 and 8.5 months, respectively. Univariate and multivariate analyzes determined that low HRR was an independent predictor of poor prognosis for OS. In our study, the prognostic significance of HRR in SCLC patients was evaluated. Our study was conducted with a larger number of patients (840 patients). OS of the patients was found to be 9 months and PS was found to be 7 months. When the patients were examined according to the determined cut-off value (<1.08), it was found that each one-unit increase in HRR reduced mortality by 1.6-fold, and each one-unit increase in HRR reduced progression by 1.62-fold.

There are studies on NLR and PLR as markers that can be used as prognostic factors in lung cancer (5, 21). However, in our study NLR and PLR values were not statistically significant in relation to OS and PS in SCLC patients.

HRR is a very easy, repeatable and inexpensive test if chronic inflammatory diseases and autoimmune diseases can be excluded. In our opinion, the fact that patients with these diagnoses were not included in our study conducted by screening a very large patient population (1039 patients) increases the importance of our study. While a large number of patients is the other strength of our study, however, there are a few limitations. First, it is a single-center retrospective study, and second, there is no standard cut-off value that can be compared in the literature.

CONCLUSION

Our study shows that HRR value is a prognostic factor and may be predicted survival in SCLC patients. However, prospective studies are needed to show the relationship of HRR with OS and PS as independent factors, considering all the factors affecting the HRR value.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences, Ankara Atatürk Sanatoryum Training and Research Hospital Clinical Researches Ethics Committee (Date: 22.02.2023, Decision No: 2661).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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